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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,116	09/26/2001	Ekambar R. Kandimalla	HYZ-479CP (47508.577)	3956
32254	7590	11/16/2006	EXAMINER	
KEOWN & ASSOCIATES 500 WEST CUMMINGS PARK SUITE 1200 WOBURN, MA 01801			LE, EMILY M	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	09/965,116		KANDIMALLA ET AL.	
	Examiner		Art Unit	
	Emily Le		1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09/05/2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,7,8 and 39-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-2,7,8 and 39-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Claims 3-6 and 9-38 are cancelled. Claims 1-2, 7-8 and 39-43 are pending and under examination.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-2, 7-8 and 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Nguyen et al.¹

In response to the rejection, Applicant submits that Nguyen et al. does not teach modified phosphorothioate or phosphorodithioate backbone.

Applicant's submission has been considered, and the rejection of the claims under 35 U.S.C. 102(b) as being anticipated by Nguyen et al. is withdrawn.

4. Claims 1-3 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Tardy-Planechaud et al.²

In response to the rejection, Applicant submits that Tardy-Planechaud et al. does not teach modified phosphorothioate or phosphorodithioate backbone.

¹ Nguyen et al. Modification of DNA duplexes to smooth their thermal stability independently of their base content for DNA sequencing by hybridization. Nucleic Acids Research, 1997, Vol. 25, No. 15, 3059-3065.

² Tardy-Planechaud et al. Solid phase synthesis and restriction endonucleases cleavage of oligodeoxynucleotides containing 5-(hydroxymethyl)-cytosine. Nucleic Acids Research, 1997, Vol. 25, No. 3, p. 553-558.

Applicant's submission has been considered, and the rejection of the claims under 35 U.S.C. 102(b) as being anticipated by Tardy-Planechaud et al. is withdrawn.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims are 1-2, 7-8 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al.³

Previously, claims 1-2, 7-8 and 42 were rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz. However, in response to the rejection, Applicant amended the claims requiring the oligonucleotide to have a modified phosphate backbone, wherein the modified backbone is either phosphorothioate or phosphorodithioate. Additionally, Applicant submits that the modified immunostimulatory oligonucleotide of Schwartz is not the same as Applicant's, since the teachings of Schwartz are directed at the modification of cytosine at the C-5/6 positions.

Regarding Applicant's second submission has been considered, however, it is not found persuasive. In the instant, the teachings of Schwartz are not solely limited to the modification of cytosine at the C-5/6 positions, as evidenced by claim 4 of Schwartz. In claim 4, Schwartz teaches that the modified cytosine can be uracil. In the instant, the

³ Schwartz, David. WO 99/62923, Published December 19, 1999.

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C-5/6 positions of cytosine and uracil are the same. Hence, Applicant's second submission is not found persuasive.

In the instant, the claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2-deoxyguanosine or a guanosine analog.

Claim 3 also requires that the pyrimidine be linked to the purine via an internucleotide linkage selected from the group consisting of phosphorothioate and phosphorodithioate; the pyrimidine nucleoside has the formula (I):



wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine.

The claims, claims 7-8 and 42 also require the pyrimidine nucleoside to comprise a non-naturally occurring sugar moiety, which is later limited to arabinose or arabinose derivatives; which is later specified as aracytosine.

Schwartz teaches an immunomodulatory oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine aracytosine and purine is guanosine. The oligonucleotide compound of Schwartz comprises aracytosine. Aracytosine is not a cytidine or deoxycytidine. Aracytosine has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. The pentose sugar ring of aracytosine is a non-naturally occurring sugar moiety, arabinose. [See claim 4 of Schwartz]

The difference between the claimed oligonucleotides and the oligonucleotides of Schwartz is: it is not readily apparent if the oligonucleotides of Schwartz comprise a phosphorothioate or phosphorodithioate. However, Schwartz et al. teaches the use of phosphorothioate linkages in place of phosphodiester linkages. Schwartz et al. notes that phosphorothioate linkages can be more immunogenic than phosphodiester linkages, and are more resistant to degradation. [First full paragraph of page 12 of Schwartz et al.] Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use phosphorothioate linkages. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to i) enhance the immunogenicity of the immunostimulatory oligonucleotide and/or ii) increase the half-life of the oligonucleotide. One of ordinary skill in the art at

the time the invention was made would have had a reasonable expectation of success for doing so because the modification of immunostimulatory oligonucleotides with phosphorothioate linkages is well practiced in the art.

7. Claims are 1-2, 7-8 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nguyen et al. in view of Schwartz et al.

The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-alkylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2'-deoxyguanosine and a guanosine analog. The claims require the pyrimidine be linked to the purine via an internucleotide linkage selected from the group consisting of phosphorothioate, and phosphorodithioate.

Nguyen et al. teaches several oligonucleotide compounds comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is linked to the purine via a phosphodiester. The oligonucleotide compounds of Nguyen et al. are at least 6 nucleotides in length. [First full paragraph, left column on page 3061; Figure 2, and Tables 1-3.]

The pyrimidine nucleoside present in one of the oligonucleotide compound of Nguyen et al. is aracytosine, wherein the aracytosine is linked guanosine. The pentose sugar ring of aracytosine is a non-naturally occurring sugar moiety, arabinose. Aracytosine is not a cytidine or deoxycytidine, and have a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen

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bond acceptor, S is a pentose sugar ring, and X is nitrogen. And this particular oligonucleotide compound comprises guanosine.

The other oligonucleotide compounds that Nguyen et al. teaches comprise N4-ethylcytosine, which is an N4-alkylcytosine, as the pyrimidine, wherein the N4-ethylcytosine is linked guanosine and a guanosine analog (adenine), separately. N4-ethylcytosine is not a cytidine or deoxycytidine, and have a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a hexose sugar ring, and X is nitrogen.

In the instant, Nguyen et al. teaches oligonucleotide compounds that are the same as those instantly claimed. The oligonucleotide composition of Nguyen et al. has the same structural characteristics as the claimed invention, with the exception that Nguyen et al. does not teach a modified phosphorothioate or phosphorodithioate backbone. The backbone that Nguyen et al. teaches is phosphodiester, rather than phosphorothioate or phosphorodithioate backbone.

However, the deficiency noted of Nguyen et al. is fully compensated by the teachings of Schwartz et al. Schwartz et al. teaches the use of phosphorothioate linkages in place of phosphodiester linkages. Schwartz et al. notes that phosphorothioate linkages can be more immunogenic than phosphodiester linkages, and are more resistant to degradation. [First full paragraph of page 12 of Schwartz et al.]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use phosphorothioate linkages. One of ordinary skill

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in the art at the time the invention was made would have been motivated to do so to i) enhance the immunogenicity of the immunostimulatory oligonucleotide of Nguyen et al., and/or ii) increase the half-life of the oligonucleotide of Nguyen et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the modification of immunostimulatory oligonucleotides with phosphorothioate linkages is well practiced in the art.

Additionally, as stated in the previous office action, it is recognized that Nguyen et al. does not comment on the immunostimulatory activity of the oligonucleotide compounds that Nguyen et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)”. Hence, Applicant’s discovery of a previously unappreciated property, the immunostimulatory property of the oligonucleotide compounds of Nguyen et al., of the prior art composition does not render the old composition patentably new to the Applicant. Thus, the claimed composition is obvious over the teaching of Nguyen et al. in view of Schwartz et al.

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8. Claims are 1-2 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tardy-Planechaud et al. in view of Schwartz et al.

The claims are directed to an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a pyrimidine nucleoside selected from the group consisting of 5-hydroxymethylcytosine, N4-ethylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine, 2'-deoxyguanosine or a guanosine analog. The claims also require the pyrimidine to be linked to the purine via an internucleotide linkage selected from the group consisting of phosphorothioate, and phosphorodithioate.

Claim 3 requires the pyrimidine nucleoside to have the formula (I):



wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that the pyrimidine

nucleoside of formula (I) is not cytidine or deoxycytidine. Claim 40 later limits the pyrimidine nucleoside to 5-hydroxymethylcytosine.

Tardy-Planechaud et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is linked to adenine, a guanosine analog via a phosphodiester. [Test sequence disclosed on page 555.] The oligonucleotide compound of Tardy-Planechaud et al. is at least 6 nucleotides in length. The pyrimidine nucleoside present in the oligonucleotide compound of Tardy-Planechaud et al. is 5-hydroxymethylcytosine. 5-hydroxymethylcytosine is not a cytidine or deoxycytidine, and has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. In the instant, Tardy-Planechaud et al. teaches an oligonucleotide compound that is the same as those instantly claimed. The oligonucleotide composition of Tardy-Planechaud et al. has the same structural characteristics as the claimed invention, with the exception that Tardy-Planechaud et al. does not teach a modified phosphorothioate or phosphorodithioate backbone. The backbone that Tardy-Planechaud et al. teaches is phosphodiester, rather than phosphorothioate or phosphorodithioate backbone.

However, the deficiency noted of Tardy-Planechaud et al. is fully compensated by the teachings of Schwartz et al. Schwartz et al. teaches the use of phosphorothioate linkages in place of phosphodiester linkages. Schwartz et al. notes that phosphorothioate linkages can be more immunogenic than phosphodiester linkages,

and are more resistant to degradation. [First full paragraph of page 12 of Schwartz et al.]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use phosphorothioate linkages. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to i) enhance the immunogenicity of the immunostimulatory oligonucleotide of Tardy-Planechaud et al., and/or ii) increase the half-life of the oligonucleotide of Tardy-Planechaud et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the modification of immunostimulatory oligonucleotides with phosphorothioate linkages is well practiced in the art.

It is recognized that Tardy-Planechaud et al. does not comment on the immunostimulatory activity of the oligonucleotide compound that Tardy-Planechaud et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)". Hence, Applicant's discovery of a previously

unappreciated property, the immunostimulatory property of the oligonucleotide compound of Tardy-Planechaud et al., of the prior art composition does not render the old composition patentably new to the Applicant. T Thus, the claimed composition is obvious over the teaching of Tardy-Planechaud et al. in view of Schwartz et al.

9. Claims 1-2 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al.⁴ in view of Schwartz et al.

In response to the rejection, Applicant argues that Kreutzer et al. and Schwartz et al. are non-analogous arts.

In response to applicant's argument that Kreutzer et al. and Schwartz are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the references are reasonably pertinent to the particular problem with which the applicant was concerned. In the instant, Applicant's field of endeavor is immunostimulatory oligonucleotides. Schwartz et al. teaches immunostimulatory oligonucleotides. Schwartz et al. also establishes that the immunostimulatory activities of these immunostimulatory oligonucleotides are due to the CpG motif. Kreutzer et al. teaches oligonucleotides comprising the CpG motif. Thus, at the time the invention was made, it logically follows that the oligonucleotides of Kreutzer et al. have immunostimulatory activities.

Additionally, Schwartz et al. teaches the use of phosphorothioate linkages in place of phosphodiester linkages. Schwartz et al. notes that phosphorothioate linkages can be more immunogenic than phosphodiester linkages, and are more resistant to degradation. [First full paragraph of page 12 of Schwartz et al.]

Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use phosphorothioate linkages. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to i) enhance the immunogenicity of the immunostimulatory oligonucleotide of Kreutzer et al., and/or ii) increase the half-life of the oligonucleotide of Kreutzer et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the modification of immunostimulatory oligonucleotides with phosphorothioate linkages is well practiced in the art.

10. Claims are 2 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz, as applied to claim 2, in view of Merigan, Jr. et al.⁵

The significance of Schwartz, as applied to claim 2, is provided above.

Claim 43, which depends on claim 2, requires the modified cytosine to be 4-thiouracil. In the instant, Schwartz does not teach 4-thiouracil. However, Schwartz does suggest the substitution of cytosine for any modified pyrimidine or pyrimidine analogs.

Merigan, Jr. et al. teaches a modified pyrimidine. The modified pyrimidine of Merigan et al. is 4-thiouracil. Hence, at the time the invention was made, it would have

⁴ Kreutzer et al. Oxidized, deaminated cytosines are a source of C→T transitions *in vivo*. Proc. Natl.

been prima facie obvious for one of ordinary skill in the art to use 4-thiouracil as the modified pyrimidine. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to obtain an immunostimulatory oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because 4-thiouracil is expected to have the similar properties as its functional counterpart, cytosine.

Conclusion

11. No claims are allowed.
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


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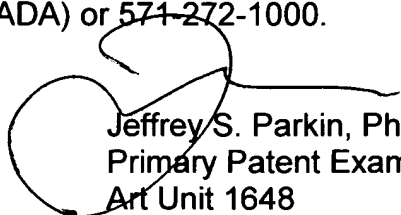
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903.

The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


E.Le
11/05/06


Jeffrey S. Parkin, Ph.D.
Primary Patent Examiner
Art Unit 1648

⁵ Merigan et al. U.S. Patent No. 3687808.